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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/550,355	11/03/2005	Maximillian Grassberger	PD/4-32803A	2105

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EXAMINER	
CHOI, FRANK I	
ART UNIT	**PAPER NUMBER**
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/550,355	GRASSBERGER ET AL.	
	Examiner	Art Unit	
	Frank I. Choi	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20070410*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 3 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for synergistic effect as it pertains to inhibition of T-cell proliferation, it does not reasonably provide enablement for a claim that reads on any synergistic effect. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The nature of the invention:

The invention is directed to a method of treatment of a dermatological disease or inflammatory bowel disease in a subject suffering from or at risk for such condition, comprising co-administering a synergistically effect amount of the combination of a macrolide T-cell immunomodulator or immunosuppressant and a calcitrol.

The state of the prior art and the predictability or lack thereof in the art:

The prior art discloses that rapamycin and 1,25(OH)2D3 act synergistically as a immunosuppressive agent in the suppression of T-cell proliferation, however, the prior art does not provide evidence that the same when applied to a dermatological disease or inflammatory bowel disease would act synergistically with respect to treatment of the disease. The prior art does not provide evidence that other combinations of a macrolide and a calcitrol would act synergistically with respect to treatment of said diseases. As such, predictability in the art

appears to be low as to whether a given combination would act synergistically with respect to a given dermatological disease or inflammatory bowel disease.

The amount of direction or guidance present and the presence or absence of working examples:

The Specification discloses a method for determining synergy, however, there is no evidence presented which shows what combinations or amounts if any acted synergistically with respect to treatment of the claimed diseases. See Ex Parte Quandranti, 25 USPQ2d 1071, 1072, 1073 (the facts shown must be analyzed to determine whether the method chosen to establish synergism clearly and convincingly demonstrates the existence of synergism, or more generally an unobvious result). Since no facts have been presented which establish that the compounds act synergistically with respect to the disease, the existence of synergism has not been clearly and convincingly demonstrated.

The breadth of the claims and the quantity of experimentation needed:

The claim is broad in that it claims any combination of a macrolide and a calcitrol and it potentially covers any person as there no minimum threshold as to which patients may be a risk for a given dermatological disease or inflammatory bowel disease. Further, the claims do not indicate what the effect is in the synergistically effective amount, and, thus is open to any synergistic effect which might occur as a result of the combination of a macrolide and a calciferol, As such, one of ordinary skill in the art would be required to do due undue experimentation in order to determine what combinations and amounts would result in a synergistic effect, including whether the combination is synergistically effective with respect to treatment of the disease.

The Examiner notes that the fact that claim 3 has been rejected as being obvious does not enable the entire scope of the claim. The prior art rejection below is based on the interpretation of the claim as being open-ended with respect to the synergistic effect, whereas the synergistic effect in the prior art rejection below is directed to inhibition of T-cell proliferation. Since Applicant has not provide other evidence which supports the full scope the claim and "synergistically effective" encompasses any synergistic effect that might occur because of the combination, the prior art rejection below does not provide evidence which supports enable of the entire scope of the claim.

The Examiner had duly considered the Applicant's arguments but deems them unpersuasive. The amendment does not address the fact that the Applicant has not shown that the claimed composition acts synergistically with respect to the claimed conditions.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 4 recites the limitation "a calciferol". There is insufficient antecedent basis for this limitation in the claim as the term "a calciferol" is not limited to "calcipotriol or tacalcitol".

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1,3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Etten et al. in view of WO 98/18468, Nghiem et al., Paul et al., Baumann et al. (US Pat. 5,912,238), Van De Kerkhof et al. and Koo et al. (US 2004/0202706).

Van Etten et al. disclose the combination of rapamycin or FK 506, which are T-cell immunosuppressants, and Vitamin 1,25(OH)2D3 or the analogs of said vitamin , TX527, ZG 1423 and WU 515, in stock solutions diluted in peanut oil for in vivo use and in stock solutions in ethanol diluted in culture medium for in vitro use, which combinations acted synergistically to suppress T-cell proliferation (Pages 1932,1934,1936-1940). It is disclosed that due to its additional immunomodulating effects on other cell types of the immune system, said vitamin and especially its analogues are potent immunomodulatory drugs which can extend the therapeutic window of classical immunomodulators in the treatment of autoimmune diseases (Page 1940). A method of determining the synergistic effect of two drugs is disclosed (Page 1935). It is disclosed that 1,25(OH)2D3 has undesired calcemic effects and that it is preferred to use analogues of 1,25(OH)2D3 which have relatively lower calcemic effects (Page 1938).

WO 98/18468 disclose that the combination of rapamycin and 1,25(OH)2D3 is useful in treating disease or disorders involving the immune system, including psoriasis, dermatitis, eczema and inflammatory bowel disease (Page 8, lines 25-36). It is disclosed that the

combination can be formulated with a pharmaceutical carrier in amounts of 0.1-5%, preferably 2%, of active compound in topical vehicles (Page 9, lines 15-36, page 10).

Nghiem et al. disclose that Tacrolimus (FK506) and Pimecrolimus (SDZ ASM 981) are structurally similar macrolide immunosuppressants and are both topically effective in treating atopic dermatitis and that ointments containing 0.2%, 0.6% and 1% of pimecrolimus and ointments containing 0.03% or 0.1% of tacrolimus have been tested (Pages 228, 229, 231-235, 240, note 26,27,28). The chemical structure of Tacrolimus and Pimecrolimus is disclosed (Page 229).

Paul et al. disclose that ascomycin derivatives, such as SDZ ASM 981, represent a novel class of ant-inflammatory macrolactams and that SDZ ASM 981 has been shown to be effective in the treatment of atopic dermatitis, contact dermatitis and psoriasis (See entire reference).

Baumann et al. disclose that FK506 and 33-epi-33-chloro-FR 520 (the Examiner notes that the structure of 33-epi-33-chloro-FR 520 corresponds the structure of pimecrolimus disclosed in Nghieim et al.) are effective in the treatment of autoimmune diseases and inflammatory and hyperproliferative skin diseases, including psoriasis, atopical dermatitis, contact dermatitis, and acne, in amounts of 1-3% for topical use in a pharmaceutically acceptable carrier (Column 11, lines 35-68, Column 29, lines 1-65, Column 30, line 24).

Van De Kerkhof et al. disclose that calcipotriol and tacalcitol have less hypercalcaemic activity than vitamin D3 and are now well-accepted and are becoming a mainstay of antipsoriatic treatment (Page 415). A study is disclosed in which a tacalcitol ointment (4 micrograms/g) was used to treat chronic plaque psoriasis in daily amounts of 5g or less, greater than 5g to 7g or greater than 7g to 13g /day in which was effective and did not clinically or statistically alter

serum calcium (Pages 415-419). It is disclosed that a previous study comparing calcipotriol ointment (50 micrograms/day, twice daily) and tacalcitol ointment showed that both treatments were effective and safe and did not significantly effect calcium metabolism (Page 420).

Koo et al. disclose the use of dermatological agents, including a vitamin D derivatives, calcipotriol, pimecrolimus and tacrolimus, and combinations thereof (Paragraph 0034). It is disclosed that the topical formulations of a dermatological agent may be in kits with instructions for use (Paragraphs 0060-0065).

The prior art discloses the combination of a macrolide T-cell immuomodulator and a calciferol with a pharmaceutical carrier. The difference between the prior art and the claimed invention is that the prior art does not expressly disclose the combination of 33-epichloro-33-desoxyascomycin and calcipotriol or tacalcitol, a method of treatment of a dermatological disease or inflammatory bowel disease with a macrolide T-cell immuomodulator and a calciferol in synergistically effective amounts or a kit of parts separately containing the same in unit dosage forms with instructions for use. However, the prior art amply suggests the same as the prior art discloses the combination of rapamycin and 1,25(OH)2D3 is use for the treatment of psoriasis, dermatitis, eczema and inflammatory bowel disease, that rapamycin or FK506 combined with 1,25(OH)2D3 or analogues thereof are synergistically effective in suppressing T-cell proliferation, that FK506 and pimecrolimus are structurally similar macrolide immunosuppressants which are effective in the treatment of dermatological diseases, including psoriasis, that calcipotriol and tacalcitol do not cause undesired effects on calcium metabolism as opposed to 1,25(OH)2D3 and that dermatological agents, such as vitamin D derivatives, calcipotriol, pimecrolimus and tacrolimus, and combinations thereof, can be in the form kits. As

such, it would have been well within the skill of and one of ordinary skill in the art would have been motivated to modify the prior art as above with the expectation that due to similar structure and effect on dermatological disease, that pimecrolimus (also referred to as 33-epichloro-33-desoxyascomycin in the Specification at page 3) would be a suitable substitute for rapamycin or FK506 and act synergistically in the inhibition of T-cell proliferation in combination with 1,25(OH)2D3 and analogues thereof, that due to their similar structure with 1,25(OH)2D3, effect on psoriasis and no effect on calcium metabolism, that calcipotriol or tacalcitol would be a suitable and preferred substitute for 1,25(OH)2D3, that the combination of pimecrolimus and calcipotriol or tacalcitol would be effective in the treatment of dermatological diseases and inflammatory bowel disease similar to the combination of rapamycin and 1,25(OH)2D3, and that dermatological agents can be conveniently packaged into kits with instructions for use.

The Examiner has duly considered the Applicant's arguments but deems them unpersuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The Supreme Court in KSR International Co. v. Teleflex Inc., held the following:

(1) the obviousness analysis need not seek out precise teachings directed to the subject matter of the challenged claim and can take into account the inferences and creative steps that one of ordinary skill in the art would employ;

(2) the obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents;

(3) it is error to look only the problem the patentee was trying to solve-any need or problem known in the filed of endeavor at the time of invention and addressed by the prior art can provide a reason for combining the elements in the manner claimed;

(4) it is error to assume that one of ordinary skill in the art in attempting to solve a problem will be led only to those elements of prior art designed to solve the same problem-common sense teaches that familiar items may have obvious uses beyond their primary purposes, and in many cases one of ordinary skill in the art will be able to fit the teachings of multiple patents together like pieces of a puzzle (one of ordinary skill in the art is not automaton);

(5) it is error to assume that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try". KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385, 1396, 1397 (U.S. 2007).

Nothwithstanding the Applicant's arguments as to the references individually, as indicated above, the prior art suggests the combination of pimecrolimus and calciptriol or tacalcitol. The prior art discloses that pimecrolium is a T-cell immunomodulater similar to rapamycin and FK506 and that rapamycin and FK506 can be combined with vitamin D derivatives and that pimecrolimus is effective in treating psoriasis. Both calcipotriol and tacalcitol are disclosed to be effective in treating psoriasis, as such, one ordinary skill in the art would expect that the combination of pimecrolimus and calipotriol or tacalcitol would also be effective in treating psoriasis.

Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of the references.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

A facsimile center has been established in Technology Center 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier number for accessing the facsimile machine is 571-273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Choi whose telephone number is (571)272-0610. Examiner maintains a compressed schedule and may be reached Monday, Tuesday, Thursday, Friday, 6:00 am – 4:30 pm (EST).

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Johann R. Richter, can be reached at (571)272-0646. Additionally, Technology Center 1600's Receptionist and Customer Service can be reached at (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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12/10/2007

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12/11/07